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1. Introduction

Early recognition of nutritional optic neuropathy is essential to avoid irreversible atrophy of the optic nerves and blindness. The disorder is characterised by slowly progressive or subacute bilateral and symmetrical visual impairment with loss of central visual acuity, centrocecal visual field defects, dyschromatopsia, temporal optic disc pallor and loss of nerve fibres in the maculopapillar bundle. Several micronutrients are required for normal optic nerve function, particularly those in the B vitamin group and copper [1, 2]. The importance is that nutritional optic neuropathy is a treatable condition, and visual loss can be reversed if adequate supplementation is given early in the disease. However, cases of nutritional optic neuropathy are often missed if a diet history is not taken and if diagnostic testing is limited to checking vitamin B12 and folate levels.

Key words: Vitamin A, Vitamin B, Copper, Diet, Malabsorption, Nutrition, Optic Neuropathy, Toxic-Nutritional Amblyopia

2. Causes of nutritional optic neuropathy (summarised in Table 1)

Micronutrient deficiencies are common, affecting an estimated 2 billion people worldwide [3]. Vitamin A, folate and iron deficiencies are the most common micronutrient deficiencies globally, and vitamin A deficiency is the most common cause of blindness due to inadequate nutrition [3]. Vitamin A deficiency causes xerophthalmia, keratomalacia, night blindness, and loss of peripheral vision [4]. Night blindness and loss of peripheral vision are early signs of vitamin A deficiency because retinol is a component of the light-sensitive retinal pigment, rhodopsin, found mainly in rod photoreceptors [5].

In contrast to vitamin A-deficient retinopathy, nutritional optic neuropathies predominantly affect central and color vision [1, 2]. The main deficiencies that cause nutritional optic neuropathy include vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin B_3 (niacin), vitamin B_6 (pyridoxine), vitamin B_9 (folate) vitamin B_{12} (cobalamin), and copper, which all have various roles in mitochondrial metabolism [1, 2]. Retinal ganglion cells contribute 1.2million axons to the retinal nerve fibre layer and optic nerve, and proportionally more small nerve fibres than large nerve fibres are located in the macula than in the peripheral retina, which might explain why the maculopapillar axon bundle is particularly vulnerable to metabolic insults, leading to central visual loss and dyschromatopsia [6].

In low- and middle-income countries, inadequate food intake is the main cause of nutritional optic neuropathy. For example, epidemics of optic neuropathy have been linked to poverty and deprivation in developing and war-torn countries, most notably, Cuba in 1992-1993, where >50,000 cases were linked to deficiencies of B vitamins, especially folate, following the economic embargo of Cuba by the US [7], and in Somalia following prolonged drought and civil war [8]. The Cuban epidemic was notable since a large task force of international experts from 55 institutions were mobilised to investigate whether there was an infectious agent, neurotoxin or other aetiology that was responsible for the large numbers of cases. Ultimately, the epidemic was chiefly attributed to dietary deficiencies of B vitamins in the absence of overt malnutrition since: (i) the economic embargo resulted in the limited supply of chicken, fish, eggs and dairy products (major sources of B vitamins) and

greater dependency on carbohydrates (which increase metabolic demand for thiamine); (ii) the epidemic appeared to spare children, pregnant women and elderly people who had been targeted by nutritional supplementation programs in Cuba since the 1970s; (iii) the majority of patients markedly improved following treatment with intravenous B vitamins including folate; and (iv) the epidemic decreased following the distribution of oral multivitamins to the entire population [7, 9].

Micronutrient deficiencies also exist in high-income countries like the US and UK, where vitamin B12 deficiency affects 6% of the population >65 years [10]. The most common cause of vitamin B12 deficiency in developed countries is malabsorption due to pernicious anaemia [11]. Pernicious anaemia is an autoimmune gastritis, associated with antibodies to intrinsic factor, in which gastric parietal cells are destroyed. Additionally, vitamin B12 deficiency is prevalent in the elderly due to progressive atrophy of the gastric mucosa [10]. Purely dietary causes of vitamin B12 deficiency are less common but may become increasingly prevalent with the rising popularity of veganism. Vegans are especially prone to vitamin B12 deficiency because fortified foods, like cereals, and animal-source foods, like fish, meat, eggs and dairy, are the main dietary sources of vitamin B12; hence, strict veganism can lead to irreversible blindness [12].

Among people with malabsorption syndromes other than pernicious anaemia, multiple micronutrient deficiencies may co-exist. For example, celiac disease, inflammatory bowel disease and, in recent decades, people who have undergone bariatric surgery are all at risk of developing multiple nutritional deficiencies that affect vision, including A and B vitamins and copper [13-15]. Purely dietary causes of nutritional optic neuropathy are less common in developed countries but can also result in multiple combined nutritional deficiencies [16]. For example, many individuals profess to follow restrictive diets of various sorts to promote their health, but actually have an underlying eating disorder [17]. Children on the autism spectrum are particularly prone to restrictive eating behaviours [18]. It is important to remember that any diet limited to only a few food types can lead to multiple nutritional deficiencies despite an adequate calorie intake. Hence, body mass index is not a good indicator of nutritional status [16].

Heavy alcohol consumption and smoking are risk factors for “toxic-nutritional amblyopia” which overlaps with nutritional optic neuropathy. Alcohol and tobacco smoke (carbon monoxide, cyanide) may have directly toxic effects on the optic nerve [15, 19-21]. Alcohol also interferes with absorption by the gastric mucosa. Furthermore, chronic alcoholics are prone to multiple deficiencies due to their poor diet, particularly of thiamine, folate, magnesium and vitamin C [15, 22-24], and it is possible that some of the toxic effects of alcohol are, in fact, mediated by thiamine deficiency [15, 24].

Several drugs, like alcohol, can lead to nutritional deficiencies because they interfere with absorption by the gastric mucosa, e.g. proton pump inhibitors, H_2 histamine receptor blockers, and metformin [11]. In other cases, people with subclinical nutritional deficiencies may be more susceptible to the toxic effects of certain drugs which interfere with the function of those micronutrients in their metabolic pathways. For example, several medications are implicated in the development of pyridoxine deficiency, such as isoniazid which increases the excretion of pyridoxine and inhibits the activation of pyridoxine by

phosphokinase [15]. Recreational nitrous oxide (NO) abuse has become an increasingly common cause of functional B12 deficiency in people with low normal serum vitamin B12 levels [11, 15, 25]. Indeed, recreational nitrous oxide abuse has been reported to precipitate vitamin B12 deficiency in otherwise normal people [25]. Moreover, treatment with vitamin B12 supplementation and cessation of exposure to nitrous oxide leads to recovery [25]. NO is sold legally in metal canisters used as propellants for whipped cream production ("whippits") and induces rapid onset euphoria. NO is also used as an anaesthetic. But, NO oxidises methylcobalamin, which impairs the enzyme methionine synthase from converting homocysteine to methionine. Thus, high serum homocysteine levels indicate functional vitamin B12 deficiency in people with consistent clinical signs, drug history and normal vitamin B12 levels[11].

Table 1

Causes of nutritional optic neuropathy		**Relevant investigations**
Inadequate intake	1. Poverty 2. Strict veganism 3. Eating disorder, e.g. anorexia nervosa, orthorexia nervosa, avoidant restrictive food intake disorder	1. Diet history 2. Blood tests for nutritional deficiencies
Malabsorption	1. Pernicious anaemia 2. Celiac disease 3. Inflammatory bowel disease 4. Atrophic gastritis 5. Gastric bypass surgery	1. Previous medical history 2. Gastric/intestinal biopsy 3. Blood tests for: a. Intrinsic factor antibodies b. IgA Tissue transglutaminase antibodies or IgA endomysial antibodies c. Nutritional deficiencies
Drugs	1. Nitrous oxide (recreational or anaesthetic) 2. Metformin 3. Antacids, e.g. proton pump inhibitors, H_2 histamine receptor blockers 4. Alcohol + smoking + poor diet	1. Drug history 2. Blood tests for nutritional deficiencies

2. Differential diagnosis of bilateral, symmetrical central visual loss and dyschromatopsia

The clinical presentation of bilateral, symmetrical central visual loss, dyschromatopsia, temporal optic disc pallor and loss of nerve fibres in the maculopapillar bundle is typically caused by disorders of mitochondrial metabolism that preferentially affect the small fibres of the optic nerve [1]. Indeed, nutritional, hereditary, and toxic insults to mitochondrial

metabolism lead to almost identical clinical presentations; the only differences between them are their speed and age of onset [1].

Nutritional optic neuropathy is mainly identified by taking a diet history and then confirmed by subsequent tests (see below). Hereditary causes of metabolic optic neuropathy, including Leber's Hereditary Optic Neuropathy or autosomal dominant optic atrophy, e.g. due to *OPA1* gene mutations, may be suggested by family history and confirmed by genetic tests. Moreover, several medications are known to be toxic to the optic nerve or act synergistically with subclinical nutritional deficiencies (e.g. alcohol, smoking, ethambutol, isoniazid, nitrous oxide), and they are normally identified by taking a drug history.

Cone dystrophies can also present with progressive central visual loss and dyschromatopsia but can be distinguished from optic neuropathy by tests of visual electrophysiology (electroretinogram, visual evoked potentials) and optical coherence tomography of the macula and optic disc showing prominent cone dysfunction and relative sparing of optic nerve structure and function.

3. Diagnostic tests

There are two reasons why testing for micronutrient deficiencies still represents a major challenge in the diagnosis of nutritional optic neuropathy:

1. Many tests are not routinely available to most clinicians, other than tests for vitamin B12 and folate.
2. Many micronutrient assays are unreliable in the lower range.

Of the vitamins that are implicated in nutritional optic neuropathy, tests for folate and vitamin B12 are the most commonly requested and widely available. Other tests for micronutrient deficiencies depend on local availability, some require special precautions (e.g. whole blood samples for thiamine need to be protected from light, serum samples for homocysteine need to be transported on ice) and since awareness of less common causes of nutritional optic neuropathy may be low, e.g. copper, some tests are not requested even when available. Consequently, many nutritional deficiencies may be missed.

The danger is when normal vitamin B12 and folate results are used to exclude a nutritional cause for optic neuropathy. Clearly, other micronutrients are implicated (see above), but also assays for vitamin B12 and folate are notoriously unreliable in the lower range. For example, the reference range for vitamin B12 depends on the assay and presence of intrinsic factor antibodies [11]. The accuracy of red cell or serum folate levels similarly depends on other factors, like co-existent vitamin B12 deficiency, haemodialysis, and haematocrit [26]. Consequently, normal vitamin B12 and folate results do not exclude a nutritional aetiology and diet history is a far better indicator.

Without taking a diet history, it is likely that many treatable cases of nutritional optic neuropathy will be missed. But, taking a good diet history does not simply depend on asking someone whether they have a "normal diet". A good starting point might be to ask, "what did you have to eat in the last 24 hours?" and then to ask about diet at the time that

symptoms first began to develop. It only takes a few minutes to ask about food frequency, e.g. “how many times a week do you eat red meat?” and to document this information in a food frequency questionnaire [27]. Given the links between diet and cardiovascular disease, obesity, dementia and cancer, taking a diet history routinely during every clinical consultation represents an opportunity to change the behaviour of our patients to improve their health: the rationale is similar to taking a smoking or alcohol history. It is far better to try to change eating behaviour and supplement a poor diet presumptively based on diet history, than to rely on the results of blood tests alone.

4. Management and prognosis

Most cases of nutritional optic neuropathy will require multidisciplinary care. This might involve ophthalmology, gastroenterology, clinical psychology, clinical biochemistry, general practice, dietetics and other specialists to arrive at the diagnosis and formulate a management plan. The treatment strategy will inevitably involve avoiding drugs and medications which are harmful to the optic nerve, while replacing micronutrients and changing eating behaviour. Clearly, cases with an underlying eating disorder and/or alcohol/drug dependency also need psychological support to change lifestyle and behaviour.

People affected by nutritional optic neuropathy often have multiple micronutrient deficiencies and deciding on the most appropriate replacement therapy and dietary changes requires specialist advice from a dietician. In some instances, parenteral replacement may be more appropriate than oral supplements, particularly for people affected by malabsorption, e.g. intramuscular injections of vitamin B12 for pernicious anaemia.
The importance is that visual loss from nutritional optic neuropathy can be reversed if it is treated early enough with replacement therapy via an appropriate route of administration.

In conclusion, nutritional optic neuropathy is a treatable condition, and visual loss can be reversed if adequate supplementation is given early in the disease. However, the diagnosis is often missed without a diet history. Asking patients about their diet should be a routine part of every clinical consultation and represents an opportunity to change behaviour to improve health.

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